

## **REMARKS**

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary correctly indicates that claims 10, 16-19, 50-56, 64-74, 76-92, 94-100, and 108-111 were pending in the application. Claims 10, 16-19, 50-56, 64-74, 76-92, 94-100, and 108-111 were considered and rejected.

Claims 19, 52, 56, 66, 70, 73, 78, 88, 94 and 99 have been canceled without prejudice or disclaimer of the subject matter described therein.

Claims 10, 50, 64, 71, 79, and 89 have been amended to recite a change during each of a sequence of incorporation cycles. Support for the amendment can be found throughout the application, for example in ¶ [0047].

Claims 18, 55, 69, 77, 87, and 98 have been amended to strike the phrase “and where FRET occurs when the two tags are in close proximity,” which was redundant because persons of ordinary skill in the art are well aware of the distance dependent nature of FRET.

No new matter has been introduced by way of the above amendments. Applicants reserve the right to file a continuation or divisional application on subject matter canceled by way of this amendment.

### **Rejections under 35 U.S.C. § 112**

Claims 10, 16-19, 50-56, 64-74, 76-92, 94-100, 102-106, and 108-111 stand rejected under 35 U.S.C. § 112, second paragraph.

In particular, claims 10, 50, 64, 71, 79, and 89 stand rejected under 35 U.S.C. § 112 as allegedly indefinite for reciting “before, during and/or after.” Applicants respectfully submit that in making the rejection, the Examiner has improperly applied a construction to the claims that a person of ordinary skill in the art would not have considered reasonable. Applicants submit that persons of ordinary skill in the art would have understood the metes and bounds of the claim as a whole. Nevertheless, and without acceding to the allegations of the rejection, Applicants have amended claims 10, 50, 64, 71, 79, and 89 to recite a change occurring during each incorporation cycle. Applicants submit that persons of ordinary skill in the art would understand the metes and bounds of the claim as amended.

Claims 19, 56, 70, 78, 88, and 99 stand rejected under 35 U.S.C. § 112 allegedly indefinite for reciting numerical values of amino acid locations. Applicants respectfully submit that when the claims were read as a whole in light of the specification as they must be, that persons of ordinary skill would have understood the metes and bounds of the claims. Nevertheless, and without acceding to any allegation of the rejection, claims 19, 56, 70, 78, 88, and 99 have been canceled. Thus, the rejection is moot.

Claims 52, 66, 73, 83, and 94 stand rejected under 35 U.S.C. § 112 for reciting SEQUENASE. Applicants respectfully submit that when the claims were read as a whole in light of the specification as they must be, that persons of ordinary skill would have understood the metes and bounds of the claims. Apart from being a trade name, SEQUENASE is an unambiguous designator for a particular well known DNA polymerase that was fully characterized at the time the application was filed.

Nevertheless, and without acceding to any allegation of the rejection, claims 52, 66, 73, 83 and 94 have been canceled. Thus, the rejection is moot.

Claims 18, 55, 69, 77, 87, and 98 stand rejected under 35 U.S.C. § 112 as allegedly indefinite for reciting “close proximity.” Applicants respectfully submit that when the claims were read as a whole in light of the specification as they must be, that persons of ordinary skill would have understood the metes and bounds of the claims. Persons of ordinary skill are well aware of the proximity requirements of FRET. Nevertheless, and without acceding to any allegation of the rejection, claims 18, 55, 69, 77, 87, and 89 have been amended to strike the phrase reciting “close proximity.” The phrase was redundant in view of the inherent proximity requirement for FRET to occur.

For at least the foregoing reasons, withdrawal of the rejections under 35 U.S.C. § 112 is appropriate and is respectfully requested.

### **Rejections under 35 U.S.C. § 103**

Claims 10, 16-19, 50-56, 64-74, 76-92, 94-100, 102-106, and 108-111 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over U.S. Patent No. 6,982,146 (Schneider et al.), in view of U.S. Patent No. 6,306,607 (Williams), and U.S. Patent No. 7,037,687 (Williams et al.)

The prior art fails to establish a proper prima facie case of obviousness. To establish a prima facie case of obviousness, there must be some motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Applicants respectfully submit that there could not have been any motivation to combine the

references as the Examiner has proposed because doing so would have been contrary to the principle of operation taught for Schneider et al and/or for Williams. It is long established that if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

The principle of operation of Schneider et al. is a FRET interaction between a donor on a polymerase and an acceptor on a nucleotide. However, the Examiner has acknowledged that Schneider et al. do not teach that the fluorescent label is released from the nucleotide by action of the polymerase and that neither Schneider et al. nor Williams et al. have been found to disclose using a nucleotide where the fluorescent label is attached to a terminal phosphate.

Williams is alleged to teach a nucleotide comprising a label attached to a terminal phosphate. However, that is not a complete description of the teachings of Williams. Williams only teaches nucleotides comprising a fluorophore attached to the  $\gamma$ -phosphate that also comprise a quencher moiety. See Williams at Abstract, col. 3, ll. 36-58. The principle of operation of Williams is detection of the fluorescent label after it is released from the quencher.

Thus, the principle of operation of the method of Schneider et al. is incompatible with the principal of operation of the method by Williams proposed to use the  $\gamma$ -phosphate labeled nucleotides. Combination of each with the other would defeat the principle of both. The presence of the quencher moiety of Williams nucleotides would

defeat the principle of FRET transfer between the donor and acceptor in the method described by Schneider et al. Modification of the Williams nucleotides to remove the quencher moiety would render the nucleotides unsuitable for their intended purpose.

Moreover, it is well established that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) Removal of the quencher moiety from the Williams nucleotides would be contrary to the principle of operation taught in Williams and would render the nucleotides unsatisfactory for their intended purpose.

Thus, either way one considers the proposed combination of Schneider et al. and Williams, there could not have been any motivation to modify the references as would be required to make the proposed combination. Williams et al. has not been alleged and does not cure these deficiencies of Schneider et al. and Williams. Therefore, the prior art does not support a prima facie case of obviousness. Consequently, withdrawal of the rejection is appropriate and is respectfully requested.

### **CONCLUSION**

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

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